

CELGENE PROPRIETARY INFORMATION

Name of Sponsor/Company: Celgene Corporation	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use Only)</i>
Name of Finished Product: Apremilast tablets	Volume: Page:	
Name of Active Ingredient: Apremilast (formerly CC-10004)		
<p>originally randomized to APR 30 BID were to remain on APR 30 BID. All subjects were to maintain APR 30 BID dosing through Week 32.</p> <ul style="list-style-type: none"> • Randomized Treatment Withdrawal Phase – Weeks 32 to 52 To evaluate the durability of response, relapse, rebound (per European Medicines Agency [EMA] guidelines), and time to relapse/loss of effect, at Week 32 subjects were assessed for Psoriasis Area and Severity Index (PASI) response and managed as follows: <ul style="list-style-type: none"> – Subjects originally randomized to apremilast at baseline (Week 0): <ul style="list-style-type: none"> o At Week 32, responders (\geq PASI-75) and partial responders (PASI-50 to PASI-74) were to be re-randomized 1:1 to maintain APR 30 BID dosing or switch to placebo (treatment withdrawal). If subjects experienced loss of response (ie, loss of 50% of the improvement of PASI score compared to baseline), they were to resume APR 30 BID treatment. Resumption of APR 30 BID treatment was to occur no later than Week 52, regardless of whether or not the subject lost response. o At Week 32, nonresponders ($<$ PASI-50) had the option of adding topical therapies and/or phototherapy to their APR 30 BID treatment regimen. The decision to add these treatments during this phase could only be made at the Week 32 visit and was based on the discretion of the investigator. – Subjects originally randomized to placebo at baseline (Week 0) and switched to APR 30 BID at Week 16: <ul style="list-style-type: none"> o At Week 32, all subjects were to maintain APR 30 BID dosing. Nonresponders ($<$ PASI-50) had the option of adding topical therapies and/or phototherapy to their treatment regimen. The decision to add these treatments during this phase could only be made at the Week 32 visit and was based on the discretion of the investigator. • Long-term Extension Phase – Weeks 52 to 260 Subjects were followed and evaluated for safety and efficacy for up to an additional 4 years (Years 2 through 5). • Observational Follow-up Phase Subjects who completed the study, or those subjects who discontinued investigational product (IP) prior to the completion of the study, were asked to participate in the 4-week Observational Follow-up Phase. 		
Number of patients (planned and analyzed): Planned: Approximately 405 Analyzed: Full analysis set: 411 Per-protocol: 400 Safety population: 408		

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Diagnosis and main criteria for inclusion:		
Subjects must have satisfied the following criteria in order to be enrolled in the study.		
<ol style="list-style-type: none"> 1. Males or females, ≥ 18 years of age at the time of signing the informed consent document 2. Understood and voluntarily signed an informed consent document prior to any study related assessments/procedures being conducted 3. Able to adhere to the study visit schedule and other protocol requirements 4. Diagnosis of chronic plaque psoriasis for at least 12 months prior to screening 5. Had moderate to severe plaque psoriasis at screening and baseline as defined by: <ol style="list-style-type: none"> a. PASI score ≥ 12; and b. Body surface area (BSA) $\geq 10\%$; and c. Static Physician Global Assessment (sPGA) ≥ 3 (moderate) 6. Was a candidate for phototherapy and/or systemic therapy 7. Was in good health (except for psoriasis) as judged by the investigator, based on medical history, physical examination, 12-lead electrocardiogram (ECG), clinical laboratories, and urinalysis 8. Met the following laboratory criteria: <ol style="list-style-type: none"> a. White blood cell count $\geq 3000/\text{mm}^3$ ($\geq 3.0 \times 10^9/\text{L}$) and $< 14,000/\text{mm}^3$ ($< 14 \times 10^9/\text{L}$) b. Platelet count $\geq 100,000/\mu\text{L}$ ($\geq 100 \times 10^9/\text{L}$) c. Serum creatinine $\leq 1.5 \text{ mg/dL}$ ($\leq 132.6 \mu\text{mol/L}$) d. Aspartate transaminase (AST) and alanine transaminase (ALT) $\leq 2 \times$ upper limit of normal (ULN) e. Total bilirubin $\leq 2 \text{ mg/dL}$ ($34 \mu\text{mol/L}$) f. Hemoglobin $\geq 9 \text{ g/dL}$ ($\geq 5.6 \text{ mmol/L}$) g. Hemoglobin A1c (HbA1c) $\leq 9.0 \%$ 9. Females of childbearing potential (FCBP) must have had a negative pregnancy test at screening and baseline. FCBP who engaged in activity in which conception was possible had to use contraception while on IP and for at least 28 days after taking the last dose of IP, where contraception was one of the following: <ol style="list-style-type: none"> a. One highly effective form (nonoral hormonal, intrauterine device [IUD], tubal ligation, vasectomized partner); or b. An oral hormonal contraceptive PLUS one additional form of barrier contraception (male or female latex condom or nonlatex condom NOT made out of natural [animal] membrane [for example, polyurethane], diaphragm with spermicide, cervical cap with spermicide, contraceptive sponge with spermicide); or c. Two forms of barrier contraception (male or female latex condom or nonlatex condom NOT made out of natural [animal] membrane [for example, polyurethane]) PLUS one 		

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<p style="text-align: center;">of the following (diaphragm with spermicide, cervical cap with spermicide, contraceptive sponge with spermicide)</p> <p>Notes:</p> <p>A female of childbearing potential was defined as a sexually mature female who: 1) had not undergone a hysterectomy (surgical removal of the uterus) or bilateral oophorectomy (surgical removal of both ovaries) or 2) had not been postmenopausal for at least 24 consecutive months (that is, had menses at any time during the preceding 24 consecutive months).</p> <p>The female subject's chosen form of contraception must have been effective by the time the female subject was randomized into the study (for example, hormonal contraception was to be initiated at least 28 days before randomization).</p> <p>10. Male subjects (including those who had a vasectomy) who engaged in activity in which conception was possible must have used barrier contraception (male latex condom or nonlatex condom NOT made out of natural [animal] membrane [for example, polyurethane]) while on IP and for at least 28 days after the last dose of IP</p> <p>The presence of any of the following excluded a subject from enrollment.</p> <ol style="list-style-type: none"> 1. Other than psoriasis, history of any clinically significant (as determined by the investigator) cardiac, endocrinologic, pulmonary, neurologic, psychiatric, hepatic, renal, hematologic, immunologic disease, or other major uncontrolled disease 2. Any condition, including the presence of laboratory abnormalities, which would have placed the subject at unacceptable risk if he/she were to have participated in the study 3. Any condition that confounded the ability to interpret data from the study 4. Pregnant or breast feeding 5. History of allergy to any component of the IP 6. Hepatitis B surface antigen positive at screening 7. Anti-hepatitis C antibody positive at screening 8. AST or ALT > 1.5 X ULN and total bilirubin > ULN and/or albumin < lower limit of normal (LLN) 9. Active tuberculosis (TB) or a history of incompletely treated TB 10. Clinically significant abnormality on 12-lead ECG at screening 11. Clinically significant abnormality based upon chest radiograph with at least posterior/anterior (PA) view (radiograph must have been taken within 12 weeks prior to screening or during the screening visit). An additional lateral view was strongly recommended but not required. 12. History of positive human immunodeficiency virus (HIV), or have congenital or acquired immunodeficiency (eg, common variable immunodeficiency disease) 13. Active substance abuse or a history of substance abuse within 6 months prior to screening 		

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<ol style="list-style-type: none"> 14. Bacterial infections requiring treatment with oral or injectable antibiotics, or significant viral or fungal infections, within 4 weeks of screening. Any treatment for such infections must have been completed at least 4 weeks prior to screening. 15. Malignancy or history of malignancy (except for treated [ie, cured] basal cell or squamous cell in situ skin carcinomas and treated [ie, cured] cervical intraepithelial neoplasia [CIN] or carcinoma in situ of the cervix with no evidence of recurrence) 16. Psoriasis flare or rebound within 4 weeks prior to screening 17. Evidence of skin conditions that would interfere with clinical assessments 18. Topical therapy within 2 weeks of randomization (including but not limited to topical corticosteroids, topical retinoid or vitamin D analog preparations, tacrolimus, pimecrolimus, or anthralin/dithranol). Exceptions: low-potency corticosteroids (Class 6 or 7) were allowed as background therapy for treatment of the face, axillae, and groin in accordance with the manufacturers' suggested usage during the course of the study. Subjects with scalp psoriasis were permitted to use coal tar shampoo and/or salicylic acid scalp preparations on scalp lesions. An unmedicated skin moisturizer (eg, Eucerin®) was permitted for body lesions only. Subjects should not have used these topical treatments within 24 hours prior to the clinic visit. 19. Systemic therapy for psoriasis within 4 weeks prior to randomization (including but not limited to cyclosporine, corticosteroids, methotrexate, oral retinoids, mycophenolate, thioguanine, hydroxyurea, sirolimus, sulfasalazine, azathioprine, fumaric acid esters) 20. Use of phototherapy within 4 weeks prior to randomization (ie, ultraviolet B light [UVB], psoralen and ultraviolet A [PUVA]) 21. Adalimumab, etanercept, infliximab, or certolizumab pegol within 12 weeks prior to randomization 22. Alefacept, briakinumab, or ustekinumab within 24 weeks prior to randomization 23. Use of any investigational drug within 4 weeks prior to randomization, or 5 pharmacokinetic/pharmacodynamic half lives, if known (whichever was longer) 24. Prolonged sun exposure or use of tanning booths or other ultraviolet (UV) light sources 25. Prior treatment with apremilast 		
Test product, dose and mode of administration, batch number: Apremilast administered orally as 10-, 20-, or 30-mg tablets Batch numbers: A list of batch numbers is provided in [REDACTED]. Apremilast 10-mg tablets: 10B0036, 10B0200 Apremilast 20-mg tablets: 10B0037, 10B0201, 10B0202 Apremilast 30-mg tablets: 10B0041, 10B0040, 10B0042, 11B0104, 10B0210, 10B206, 10B0039, 10B0211, 11B0163, 10B0239		

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<p>Duration of treatment:</p> <p>The study was designed as a 52-week study with an active-treatment, long-term extension of up to an additional 4 years (up to Week 260).</p> <p>This report presents an analysis of the final study results through Week 260 (or early termination). During the 52 weeks, subjects were to be treated with placebo or APR 30 BID for the first 16 weeks. From Weeks 16 to 32, all subjects were to receive APR 30 BID. From Week 32 up to Week 52, re-randomized subjects received placebo or APR 30 BID and non-re-randomized subjects continued to receive APR 30 BID. Subjects re-randomized to placebo at Week 32 could resume APR 30 BID prior to Week 52 if they lost response. Following the Week 52 visit, subjects could have entered a Long-term Extension Phase and received open label APR 30 BID for up to an additional 4 years (Years 2 through 5).</p>		
<p>Reference therapy, dose and mode of administration, batch number:</p> <p>Placebo administered orally as tablets identical in appearance to apremilast tablets</p> <p>Batch numbers: A list of batch numbers is provided in [REDACTED].</p> <p>Placebo 10-mg tablets: 10B0005, 10B0207, 10B0348, 11B0170, 11B0220</p> <p>Placebo 20-mg tablets: 10B0006, 10B0053, 10B0044, 10B0052, 10B0349, 11B0110, 10B0059, 10B0350, 10B0058, 10B0270, 11B0165, 11B0111</p> <p>Placebo 30-mg tablets: 10B0010, 10B0045, 10B0081, 10B0352, 10B0056, 10B0055, 10B0062, 11B0157, 10B0351, 10B0363</p>		
<p>Criteria for evaluation:</p> <p>Efficacy:</p> <p>The primary endpoint was the proportion of subjects treated with either apremilast 30 mg BID or placebo who achieved at least a 75% reduction in Psoriasis Area and Severity Index (PASI-75) at Week 16 from baseline.</p> <p>The major secondary endpoint was the proportion of subjects treated with either apremilast 30 mg BID or placebo with a static Physician Global Assessment (sPGA) score of clear (0) or almost clear (1) with at least 2 points reduction from baseline at Week 16.</p> <p>Secondary endpoints in this study were:</p> <ul style="list-style-type: none"> • Percent change from baseline in psoriasis affected BSA (%) at Week 16 • Percent change from baseline in the PASI score at Week 16 • Proportion of subjects who achieve PASI-50 at Week 16 • Change from baseline in the Pruritus Visual Analog Scale (VAS) at Week 16 • Change from baseline in the Dermatology Life Quality Index (DLQI) total score at Week 16 • Change from baseline in the Mental Component Summary (MCS) score of Medical Outcome Study Short Form 36-Item Health Survey (SF-36) at Week 16 • Proportion of subjects who achieved both PASI-75 and sPGA score of clear (0) or almost clear 		

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(1) with at least 2 points reduction from Baseline at Week 16

- Time to loss of effect (ie loss of 50% of the improvement in PASI score obtained at Week 32 compared to baseline) during the Randomized Treatment Withdrawal Phase

The exploratory endpoints in this study were:

- PASI
 - Time to achieve PASI-50 and PASI-75 during Placebo-controlled Phase
 - Proportion of subjects who achieved PASI-75 at Weeks 24, 32, and 52
 - Proportion of subjects who achieved PASI-50 at Weeks 24, 32, and 52
 - Proportion of subjects who achieved PASI-90 at Weeks 16, 24, 32, and 52
 - Percent change from baseline in the PASI score at Weeks 24, 32, and 52
- Proportion of subjects with a sPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline at Weeks 24, 32, and 52
- Percent change from baseline in percent of psoriasis affected BSA at Weeks 24, 32, and 52
- DLQI
 - Proportion of subjects who achieved a decrease of at least 5 in DLQI total score at Weeks 16, 24, 32, and 52
 - Proportion of subjects who achieved PASI-50 with a decrease of at least 5 in DLQI total score at Weeks 16, 24, 32, and 52
 - Change from baseline in DLQI total score at Weeks 24, 32, and 52
- VAS
 - Change from baseline in the Pruritus VAS at Weeks 24, 32, and 52
 - Proportion of subjects who achieved at least a 10-mm decrease in Pruritus VAS score at Weeks 16, 24, 32, and 52
 - Change from baseline in the Psoriatic Arthritis Disease Activity VAS at Weeks 16, 24, 32, and 52
 - Change from baseline in the Skin Discomfort/Pain VAS at Weeks 16, 24, 32, and 52
 - Change from baseline in the Subject’s Global Assessment of Psoriasis Disease Activity VAS at Weeks 16, 24, 32, and 52
- Health-related Quality of Life
 - Change from baseline in SF-36 scores at Weeks 16, 24, 32, and 52
 - Change from baseline in European Quality of Life-5 Dimensions Questionnaire (EQ-5D) scores at Weeks 16, 32 and 52
 - Change from baseline in Patient Health Questionnaire-8 (PHQ-8) scores at Weeks 16, 24,

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<p style="text-align: center;">32, and 52</p> <ul style="list-style-type: none"> – Change from baseline in Work Limitations Questionnaire-25 (WLQ-25) scores at Weeks 16, 32 and 52 • Nail Assessments <ul style="list-style-type: none"> – Percent change from baseline in the Nail Psoriasis Severity Index (NAPSI) score at Weeks 16, 24, 32, and 52 – Proportion of subjects who achieve a 50% reduction in NAPSI score from the baseline visit at Weeks 16, 24, 32, and 52 – Change from baseline in the number of involved nails in subjects with nail psoriasis • Scalp Psoriasis <ul style="list-style-type: none"> – Proportion of subjects with scalp psoriasis with improvement of Scalp Physician Global Assessment (ScPGA) scores to 0 and 1 at Weeks 16, 24, 32, and 52 – Proportion of subjects with scalp psoriasis with improvement of ScPGA scores to 0, 1, and 2 at Weeks 16, 24, 32, and 52 • Palmoplantar Psoriasis <ul style="list-style-type: none"> – Proportion of subjects with palmoplantar psoriasis with improvement of Palmoplantar Psoriasis Physician Global Assessment (PPPGA) scores to 0 and 1 at Weeks 16, 24, 32, and 52 – Proportion of subjects with palmoplantar psoriasis with improvement of PPPGA scores to 0, 1, and 2 at Weeks 16, 24, 32, and 52 <p>Long-term Extension Phase: For the Long-term Extension Phase, the above exploratory endpoints were similarly defined and evaluated by study visit through Week 260.</p> <p>The pharmacodynamic (PD) endpoint in this study was to explore the relationship of apremilast or placebo treatment with change in plasma biomarkers in each treatment group, compared to baseline. The PD data collected during the study are summarized in a separate report (CC-10004-PSOR-009-PD)</p> <p>Safety: Safety assessments included:</p> <ul style="list-style-type: none"> • Adverse events (AE) • 12-lead electrocardiograms (ECG) • Chest radiographs (CXR) • Physical examinations • Vital signs • Pregnancy tests • Clinical laboratory tests 		

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<ul style="list-style-type: none"> Evaluation of psoriasis flare or rebound 		
<p>Statistical methods:</p> <p>Analysis populations:</p> <p>The safety population analysis set included all subjects who were randomized and received at least one dose of IP.</p> <p>The full analysis set (FAS), defined as all subjects who were randomized as specified in the protocol, was the primary population for the efficacy analyses for the Placebo-controlled Phase. The per protocol (PP) population analysis set included all subjects included in the safety population who had at least 1 posttreatment PASI evaluation and no protocol violations. Supportive analyses using the per-protocol (PP) population were conducted for the primary endpoint and the major secondary endpoint.</p> <p>Efficacy:</p> <p>The primary efficacy analysis compared the proportions of subjects in the two treatment groups (APR 30 BID or placebo) who achieved at least a PASI-75 at Week 16 in reference to the baseline visit, using a 2-sided chi-square test at the 0.05 level. The primary analysis was based on the FAS. Missing values at Week 16 were imputed using the last observation carried forward (LOCF) method.</p> <p>To control the overall type I error rate at the 2-sided 0.05 significance, a step-down procedure was used to claim statistical significance for the primary, the major secondary, the eight other secondary, and three additional endpoints. Statistical significance for an endpoint was claimed only if its 2-sided p-value was < 0.05 and all previous tests were significant at 2-sided p < 0.05. The test sequence for efficacy endpoints was as follows:</p> <ul style="list-style-type: none"> Proportion of subjects treated with either APR 30 BID or placebo who achieved at least a PASI-75 at Week 16 from baseline Proportion of subjects treated with either APR 30 BID or placebo with an sPGA response at Week 16 Percent change from baseline in the psoriasis affected BSA (%) at Week 16 Percent change in the PASI score from the Baseline Visit at Week 16 Proportion of subjects who achieve PASI-50 at Week 16 Change from baseline in the Pruritus VAS at Week 16 Change from baseline in the DLQI total score at Week 16 Percent change from baseline in the NAPSI score at Weeks 16 for subjects with baseline nail psoriasis Proportion of subjects with improvement of ScPGA scores to clear (0) or minimal (1) with at least 2 points reduction from baseline at Weeks 16 for subjects with baseline ScPGA score moderate (3) or above Proportion of subjects with improvement of PPPGA scores to clear (0) or almost clear (1) with at least 2 points reduction from baseline at Weeks 16 (Pooled data from CC 10004-PSOR-008 and CC-10004-PSOR-009) for subjects with baseline PPPGA score moderate (3) or above 		

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<ul style="list-style-type: none"> • Change from baseline in the MCS score of SF-36 at Week 16 • Proportion of subjects who achieve both PASI-75 and sPGA score of clear (0) or almost clear (1) with at least 2 points reduction from baseline at Week 16 • Time to loss of 50% of the improvement in PASI score (loss of effect) during the Randomized Treatment Withdrawal Phase <p>Endpoints that did not meet the hierarchical criteria were considered nominally statistically significant if their 2-sided p-value was < 0.05. Other efficacy analyses were considered supportive and/or explanatory.</p> <p>The analysis of the major secondary endpoint compared the proportions of subjects in the two treatment groups (APR 30 BID or placebo) who achieved at least an sPGA at Week 16 in reference to the baseline visit, using a 2-sided chi-square test at the 0.05 level, conditional on observing a statistically significant result for the primary analysis.</p> <p>Supportive analyses were conducted for the primary endpoint and the major secondary efficacy endpoint as follows: (1) FAS treating missing values as nonresponders (nonresponder imputation [NRI]), (2) FAS using LOCF, (3) PP population using LOCF method for imputing missing values. In addition, analyses using CMH test was performed for FAS using LOCF method for imputing missing values.</p> <p>The other endpoints in the hierarchical sequence were compared using the chi-square test for discrete variables, an analysis of covariance (ANCOVA) model for continuous variables, and the log-rank test for time-to-event variables. Data were summarized using descriptive summary statistics for continuous variables (n, mean, standard deviation, median, minimum, and maximum). Frequency and percentages were provided for categorical variables. The changes or percent changes from baseline between the two treatment groups (APR 30 BID and placebo) were to be compared using an ANCOVA model with treatment as the factor and the baseline score as the covariate. Statistical evaluation of time to loss of effect (ie, loss of 50% of the improvement of PASI score obtained at Week 32 compared to baseline) during the Randomized Treatment Withdrawal Phase was based on the re-randomized treatment groups, APR 30 BID or placebo, for those subjects who were originally randomized to APR 30 BID and achieved ≥ PASI-50 at Week 32. The Kaplan-Meier procedure was used to estimate the median time to loss of effect and the log-rank test was to be used to compare the two treatment groups.</p> <p>Subgroup analyses for the primary endpoint and the major secondary efficacy endpoint based on baseline demographic (age, sex, race), baseline disease characteristics, as well as region were provided to determine the robustness of the treatment effect.</p> <p>Descriptive statistics were to be presented for exploratory endpoints. Specifically, for continuous variables, summary statistics for baseline, specified timepoints, and changes from baseline were provided. Categorical variables were summarized with frequency tabulations. The Kaplan-Meier procedure was used to characterize the time to achieve at least PASI-50 or PASI-75 during the Placebo-controlled Phase.</p> <p>Safety: For the analysis of safety, 4 phases and an Apremilast-exposure Period were used as follows: Placebo-</p>		

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<p>controlled Phase (Weeks 0 to 16), Maintenance Phase (Weeks 16 to 32), Randomized Treatment Withdrawal Phase (Weeks 32 to 52) for subjects who were re-randomized and subjects who were not re-randomized, a Long-term Extension Phase (Weeks 52 to 260), and Apremilast-exposure Period. The safety analyses for the 3 phases were performed using the safety population. Safety analyses for the Apremilast-exposure Period were performed using the Apremilast Subjects as Treated Population (all subjects who received at least one dose of apremilast).</p> <p>Adverse events were coded according to the Medical Dictionary for Drug Regulatory Activities, version 14.0. Adverse events were tabulated by phase/period. Treatment-emergent adverse events (TEAEs) were summarized by system organ class (SOC), preferred term (PT), severity, relationship to IP, and duration of treatment. Adverse events leading to death or to discontinuation from treatment and serious adverse events (SAEs) were summarized.</p> <p>Laboratory data were summarized by visit descriptively. In addition, shift tables showing the number of subjects with values low, normal, and high based on the normal ranges pretreatment versus posttreatment were provided. Hy's law criteria (AST/ALT $\geq 3 \times$ ULN plus total bilirubin $\geq 1.8 \times$ ULN) were assessed and summarized.</p> <p>Vital sign measurements, including weight, were summarized by visit descriptively. Shift tables of shifts from baseline to postbaseline timepoints, and to the worst postbaseline value in terms of normal/abnormal, were provided for pulse and blood pressure.</p> <p>The proportion of subjects in each treatment group who had a flare or rebound of their psoriasis during each study phase was provided.</p>		
<p>SUMMARY – CONCLUSIONS</p> <p>EFFICACY RESULTS:</p> <p>CC-10004-PSOR-009 was a Phase 3, double-blind, multicenter, placebo-controlled trial comprised of a 16-week Placebo-controlled Phase, a 16-week Maintenance Phase, and a 20-week Randomized Treatment Withdrawal phase, followed by an open-label, long-term safety extension phase of up to 4 additional years. This report presents an analysis of the study results through the end of the study.</p> <p>A total of 411 subjects with moderate to severe plaque psoriasis were enrolled in the study and included in the FAS. Baseline disease characteristics and medical history were similar for the two treatment groups and reflect the patient populations typically enrolled in psoriasis clinical trials. Approximately 67% of the study population was male and approximately 50% of subjects were obese, with mean weight of 91.10 kg and mean body mass index (BMI) of 30.80 kg/m². The mean baseline PASI score was 19.30, mean duration of disease was 18.19 years, and mean BSA involvement was 26.17%.</p> <p>Approximately 30% of the population had severe psoriasis at baseline (PASI > 20 [31.6%] or sPGA = 4 [30.2%]), and 54.3% of subjects had baseline BSA involvement of greater than 20%. Overall, 64.2% of subjects had been treated previously with phototherapy or systemic therapy (includes conventional systemics and biologics). In addition, 38.7% of subjects had been previously treated with conventional systemic therapies; 33.1% and 24.8% had prior exposure to biologics and TNF blockers, respectively.</p> <p>The primary endpoint of the study was met, ie, a statistically significantly greater proportion of subjects treated with APR 30 BID achieved a PASI-75 at Week 16, compared with placebo-treated subjects (5.8% placebo; 28.8% APR 30 BID; p < 0.0001). The primary efficacy analysis was supported by</p>		

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multiple sensitivity analyses that included different analysis populations (FAS and PP) and various assumptions for missing data (eg, LOCF, NRI). In addition, the primary endpoint analysis consistently demonstrated the treatment benefit of APR 30 BID, relative to placebo, across multiple demographic and disease characteristic subgroups, including baseline disease severity (moderate vs. severe psoriasis) and whether or not subjects had been treated previously with systemic (including biologics) psoriasis treatments.

The analysis of the major secondary endpoint further supported the primary efficacy analysis, ie, a statistically significantly greater proportion of subjects treated with APR 30 BID achieved an sPGA score of clear (0) or almost clear (1), with at least a 2-point reduction from baseline at Week 16, compared with placebo (4.4% placebo; 20.4% APR 30 BID; $p < 0.0001$). The major secondary endpoint analysis also consistently demonstrated the treatment benefit of APR 30 BID, compared with placebo, across multiple subgroups.

A nominally statistically significantly greater proportion of subjects treated with APR 30 BID achieved the composite endpoint, comprising both a PASI-75 response and an sPGA response at Week 16, compared with placebo-treated subjects (nominal $p < 0.0001$). Note: For the primary, the major secondary, the eight other secondary, and three additional endpoints, a step-down procedure was used to claim statistical significance. Statistical significance for an endpoint was claimed only if its 2-sided p value was < 0.05 and all previous tests were significant at 2-sided $p < 0.05$. Endpoints that did not meet the hierarchical criteria were considered nominally statistically significant if their p -value was < 0.05 .

For the majority of secondary endpoints at Week 16, subjects treated with APR 30 BID showed clinically meaningful and statistically significant improvements, compared with placebo, demonstrating the effect of apremilast on a number of disease characteristics, including clinical signs, symptoms, and quality of life. Statistically significant ($p < 0.0001$) effects of APR 30 BID, compared with placebo, were observed in percent change from baseline in BSA involvement, percent change from baseline in PASI score, proportion of subjects achieving PASI-50, change from baseline in Pruritus VAS, and change from baseline in DLQI total score. A nominally statistically significant effect of APR 30 BID, compared with placebo, was observed in change from baseline in SF-36 MCS (nominal $p = 0.0078$). The mean change from baseline in the SF-36 MCS at Week 16 in the APR 30 BID treatment group exceeded the MCID of 2.5.

Meaningful treatment benefits of APR 30 BID, compared with placebo, at Week 16 were also observed in subject self-assessments, including change from baseline in Skin Discomfort/Pain VAS [nominal $p < 0.0001$] and Subject's Global Assessment of Psoriasis Disease Activity VAS [nominal $p < 0.0001$], as well as HRQoL endpoints, such as change from baseline in EQ-5D VAS (nominal $p = 0.0002$), EQ-5D Index Value score (nominal $p = 0.0095$), and PHQ-8 total score (nominal $p = 0.0126$).

Meaningful effects of APR 30 BID, compared with placebo, were observed in difficult to treat areas of psoriasis, such as nail psoriasis (change from baseline in NAPSI score [$p = 0.0052$] and proportion of subjects with NAPSI-50 [nominal $p < 0.0001$]), scalp psoriasis (proportion of subjects with ScPGA response [improvement of ScPGA scores to 0 and 1 at Week 16], $p < 0.0001$), and palmoplantar psoriasis (proportion of subjects with PPPGA response [improvement of PPPGA scores to 0 and 1 at Week 16], nominal $p = 0.0315$).

Meaningful APR 30 BID responses occurred by Week 2 in multiple assessments, including percent

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change from baseline in PASI score, proportion of subjects achieving PASI-50, and change from baseline in Pruritus VAS, Skin Discomfort/Pain VAS, and Subject's Global Assessment of Psoriasis Disease Activity VAS.

During the Maintenance Phase (Weeks 16 to 32), PASI-75 and sPGA response rates reached a plateau around Weeks 16 to 20 for subjects originally randomized to APR 30 BID at baseline and were generally maintained throughout this phase of the study (Week 32). For subjects who switched from placebo to APR 30 BID at Week 16, PASI-75 and sPGA responses following initiation of APR 30 BID treatment were similar to those observed in subjects originally randomized to APR 30 BID during the Placebo-controlled Phase. By Week 32, the response rates for Placebo/APR 30 BID subjects following 16 weeks of APR 30 BID were similar to those observed in subjects receiving 32 weeks of APR 30 BID.

In the Randomized Treatment Withdrawal Phase (Weeks 32 to 52), subjects who were originally randomized to APR 30 BID at baseline and had at least a PASI-50 response at Week 32 were re-randomized to APR 30 BID or placebo in order to evaluate loss of response, defined as loss of 50% of the improvement in PASI score obtained at Week 32. The analysis showed that loss of response occurred significantly faster in subjects re-randomized to placebo than subjects re-randomized to APR 30 BID, ie, Kaplan-Meier estimate of median time to loss of 50% of the improvement in PASI score at Week 32 was 12.4 and 21.9 weeks following the Week 32 re-randomization in the APR 30 BID/APR 30 BID/Placebo and APR 30 BID/APR 30 BID/APR 30 BID treatment groups, respectively (nominal $p < 0.0001$). For the APR 30 BID/APR 30 BID/Placebo and APR 30 BID/APR 30 BID/APR 30 BID treatment groups, respectively, 56.5% and 11.5% of subjects lost 50% of their PASI improvement at some timepoint during the Randomized Treatment Withdrawal Phase.

In subjects re-randomized to APR 30 BID (APR 30 BID/APR 30 BID/APR 30 BID treatment group), 80.3% of subjects demonstrated a PASI-50 or greater response at Week 52. The mean percent change (improvement) in PASI score in the APR 30 BID/APR 30 BID/APR 30 BID treatment group was generally maintained following re-randomization (Week 32) through Week 52 with mean percent changes during this interval ranging from -74% to -77%. A total of 32 subjects in the APR 30 BID/APR 30 BID/Placebo treatment group lost 50% of their PASI improvement after Week 32 and resumed treatment with APR 30 BID prior to Week 52. Of these 32 retreated subjects, 65.6% achieved PASI-50 after retreatment with APR 30 BID between Weeks 34 and 52.

A total of 217 subjects entered the Long-term Extension Phase, and 48 (22.1%) subjects completed the study. Among subjects who remained on APR 30 BID in the Long-term Extension Phase, the mean percent changes in PASI score from baseline by time point were maintained from Week 52 (-64.84%) to Week 260 (-74.94%). The proportion of subjects with PASI-75 and sPGA responses analyzed using nonresponder imputation, gradually decreased during the Long-term Extension Phase. A decrease in the number of subjects completing the study over time may have affected the results of later visits. Improvements in multiple endpoints, including BSA, DLQI, and pruritus were maintained from Week 52 to Week 260.

In summary, APR 30 BID was shown to be an efficacious treatment for moderate to severe plaque psoriasis, with a rapid onset of action and a sustained effect in most subjects. Subjects treated with APR 30 BID demonstrated significant clinical benefit across the multiple parameters measured.

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SAFETY RESULTS:

During the 16-week Placebo-controlled Phase, the subject incidence of TEAEs was 68.0% for subjects treated with APR 30 BID, compared with 60.3% for subjects treated with placebo. The incidence of subjects with drug-related TEAEs was higher in the APR 30 BID treatment group (39.0%), compared with the placebo treatment group (21.3%). The proportions of subjects with severe TEAEs, SAEs, and TEAEs leading to drug withdrawal were similar between the APR 30 BID and placebo treatment groups. The most frequently reported TEAEs during Weeks 0 to 16 were GI events (diarrhea, nausea, and vomiting), infections (nasopharyngitis and upper respiratory tract infection), headache, tension headache, and psoriasis (flare or worsening). Except for psoriasis (flare or worsening), the incidence rates for these frequently reported TEAEs were higher in the APR 30 BID treatment group, compared with the placebo treatment group. However, the majority of these TEAEs were mild or moderate in severity, with severe events occurring in 4.4% of subjects in each treatment group during Weeks 0 to 16.

No new safety findings emerged during the Maintenance Phase (Weeks 16 to 32), Randomized Treatment Withdrawal Phase, or Long-term Extension Phase. The most frequently reported TEAEs, severe TEAEs, serious TEAEs, and TEAEs leading to drug withdrawal during the Maintenance Phase or the Randomized Treatment Withdrawal Phase were consistent with the Placebo-controlled Phase. Subjects who were re-randomized to placebo during the Randomized Treatment Withdrawal Phase and resumed APR 30 BID (without titration) did not appear to experience an increase in TEAEs. Nausea, diarrhea, and headache tended to occur more frequently during the first week of dosing, compared with subsequent weeks, although this was not observed in subjects who were re-randomized to placebo at Week 32 and then resumed treatment with APR 30 BID.

Similar results were observed in the Apremilast-exposure Period, which comprised the entire duration of exposure to apremilast through Week 260 (380 subjects; 674.0 subject-years). Overall, the most frequently reported TEAEs during the Apremilast-exposure Period were nasopharyngitis, nausea, diarrhea, and upper respiratory tract infection. These events did not appear to increase over time, and no TEAEs emerged with continued exposure to apremilast. The most frequently reported TEAEs, severe TEAEs, serious TEAEs, and TEAEs leading to drug withdrawal in the Apremilast-exposure Period were consistent with those in the Placebo-controlled Phase.

One death occurred during the Randomized Treatment Withdrawal Phase. The subject died due to intracranial hemorrhage (a major adverse cardiac event [MACE]) on Study Day 354, 130 days after the last dose of apremilast. The investigator considered this event as not suspected of being related to IP. One death occurred during the Long-term Extension Phase. The subject's last dose of active treatment was administered on Study Day 1370. The subject died on Study Day 1433 due to complications of chronic ethanolism that was severe in intensity. The investigator considered this event as not suspected of being related to apremilast. The incidence of SAEs through Week 260 remained low at 11.6%.

In general, for apremilast-treated subjects, rates of flare/rebound were similar or lower throughout the study, compared with the rates observed for placebo-treated subjects in the Placebo-controlled Phase (Weeks 0 to 16).

The safety analysis of TEAEs of special interest, which included infections, MACEs, malignancies, suicidal ideation and behavior, GI events, and vasculitis, revealed no new findings during the study.

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Nasopharyngitis was the only infection that occurred in $\geq 5\%$ of subjects in any treatment group during the Placebo-controlled Phase and was reported in higher subject frequency in the APR 30 BID treatment group, compared with the placebo treatment group. Infections such as nasopharyngitis and upper respiratory tract infection were among the most frequently reported TEAEs during the Apremilast-exposure Period; 7 subjects had TEAEs of infection that met serious criteria, including appendicitis (n = 2), abdominal abscess (n = 1), infectious mononucleosis (n = 1), lung abscess (n = 1), pneumonia (n = 1), and pneumonia staphylococcal (n = 1). One serious infection (appendicitis) was recorded in the Apremilast-exposure Period, which was considered by the investigator as not suspected of being related to IP. Gastrointestinal events, particularly nausea and diarrhea, accounted for the most frequently reported TEAEs during the Placebo-controlled Phase, were more frequently reported in the APR 30 BID treatment group, and were the most frequently considered by the investigator to be drug-related. However, in the APR 30 BID treatment group, diarrhea and nausea were predominantly mild in severity, had the highest incidence rate during the first week of dosing, and generally resolved within 1 month. There were no reports of severe nausea or diarrhea during the study. Serious GI TEAEs were reported in 4 subjects receiving APR 30 BID, including abdominal pain, duodenal ulcer hemorrhage, gastric ulcer, and dysphagia. Three possible MACE events were reported during the study, ie, intracranial hemorrhage resulting in death (see above), subarachnoid hemorrhage on Study Day 272 in a subject receiving APR 30 BID, and myocardial infarction resulting in permanent discontinuation of the study drug. The investigator assessed the subarachnoid hemorrhage as suspected of being related to IP; the subject recovered from the event. Four solid tumor malignancies of uterine cancer, breast cancer, endometrial cancer, and renal cell carcinoma were reported in subjects receiving APR 30 BID. The event of endometrial cancer was suspected to be related to IP. Five nonserious events of skin malignancy were reported in 4 subjects. There was 1 case of attempted suicide in a subject receiving APR 30 BID. No cases of systemic vasculitis were reported during the study.

Although there was no age effect observed with overall TEAEs, diarrhea, nasopharyngitis, tension headache, headache, and vomiting appeared to occur more frequently in subjects < 65 years of age, compared with subjects > 65 years of age, in both treatment groups. However, the small number of subjects in the ≥ 65 year age group may limit meaningful comparisons between age groups. Overall, a higher frequency of TEAEs was observed among female subjects, compared with males.

No clinically meaningful changes in hematology or clinical chemistry parameters, vital signs, or ECG findings were observed during the study. Laboratory abnormalities were mostly associated with short-term changes, generally did not lead to dose interruption or discontinuation, and did not indicate a need for regular routine laboratory monitoring. No cases of liver enzyme elevations meeting Hy's Law criteria were reported.

The majority of subjects originally randomized to APR 30 BID maintained their weight within $\pm 5\%$ of baseline in all phases of the study. Weight loss of 5% to 10% at Week 16 was observed in 13.8% and 2.5% of subjects who received APR 30 BID and placebo, respectively. At Week 32, weight loss of > 10% was observed in 5.0% of subjects who were randomized to APR 30 BID at Week 0 and in 5.8% of subjects who were switched to APR 30 BID at Week 16. At Week 52, weight loss of > 10% was reported in 6.5% subjects who were re-randomized to APR 30 BID and 7.1% subjects who were re-randomized to placebo who remained on placebo. For non-re-randomized subjects at Week 52,

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<p>weight loss of > 10% was reported in 5.6% and 4.3% of the subjects originally randomized to APR 30 BID and placebo, respectively. Three subjects in the Apremilast-exposure Period had > 20% weight loss during the study. At last assessment during the Apremilast-exposure Period, weight changes were similar to those at Week 16.</p> <p>Overall, the profile of TEAEs reported in this study, including severe TEAEs, SAEs, AEs leading to drug withdrawal, and AEs of special interest, is consistent with the known safety profile of apremilast. There was no increase in the incidence of TEAEs over time, and no unusual or unexpected safety findings emerged during the 260-week study.</p> <p>CONCLUSION:</p> <p>Apremilast demonstrated statistically significant and clinically meaningful improvements in clinical endpoints and patient-reported outcome measures. The profile of TEAEs reported in this study, including severe TEAEs, SAEs, AEs leading to drug withdrawal, and AEs of special interest, is consistent with the known safety profile of apremilast. The efficacy of apremilast has been demonstrated in subjects previously treated with phototherapy and/or systemic therapies (including biologics), as well as subjects naïve to those therapies. Apremilast may therefore provide a novel therapeutic option for the treatment of patients with moderate to severe plaque psoriasis.</p> <p>Date of the report: 30 August 2017</p>		